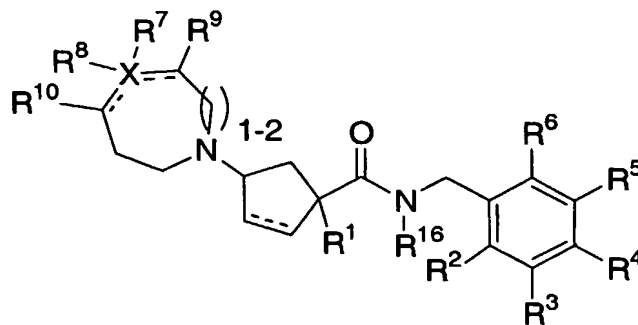


WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

X is O, N, S, SO₂ or C;

R¹ is selected from:

hydrogen, -C₁₋₆alkyl, -C₀₋₆alkyl-O-C₁₋₆alkyl, -C₀₋₆alkyl-S-C₁₋₆alkyl, -(C₀₋₆alkyl)-(C₃₋₇cycloalkyl)-(C₀₋₆alkyl), hydroxy, heterocycle, -CN, -NR¹²R¹², -N R¹²COR¹³, -N R¹²SO₂R¹⁴, -N R¹²SO₂NR¹² R¹²-, -COR¹¹, -CON R¹² R¹², and phenyl, where:

said alkyls and cycloalkyls are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C₁₋₃alkyl, trifluoromethyl, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -SO₂R¹⁴, -NHCOCH₃, -NHSO₂CH₃, -heterocycle, =O, and -CN,

said phenyl and heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy and trifluoromethyl;

R¹¹ is selected from: hydroxy, hydrogen, C₁₋₆ alkyl, -O- C₁₋₆alkyl, benzyl, phenyl, C₃₋₆ cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl,

R¹² is independently selected from: hydrogen, C₁₋₆ alkyl, benzyl, phenyl, C₃₋₆ cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl,

R¹³ is selected from: hydrogen, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl, C₃₋₆ cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl, and

R¹⁴ is selected from: hydroxy, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl, C₃₋₆ cycloalkyl where the alkyl, phenyl, benzyl, and cycloalkyl groups can be unsubstituted or substituted with 1-3 independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl;

R² is selected from:

- (a) hydrogen,
- (b) C₁₋₃alkyl, unsubstituted or substituted with 1-3 fluoro,
- (c) -O-C₁₋₃alkyl, unsubstituted or substituted with 1-3 fluoro,
- (d) hydroxy,
- (e) chloro,
- (f) fluoro,
- (g) bromo, and
- (h) phenyl;

R³ is selected from:

- (a) hydrogen,
- (b) hydroxy,
- (c) halo,
- (d) C₁₋₃alkyl unsubstituted or substituted with 1-6 substituents independently selected from: fluoro, hydroxy, and -COR¹¹,
- (e) -NR¹²R¹²,
- (f) -COR¹¹,
- (g) -CONR¹²R¹²,
- (h) -NR¹²COR¹³,
- (i) -OCONR¹²R¹²,
- (j) -NR¹²CONR¹²R¹²,
- (k) -heterocycle,
- (l) -CN,

- (m) -NR¹²-SO₂-NR¹²R¹²,
- (n) -NR¹²-SO₂-R¹⁴,
- (o) -SO₂-NR¹²R¹² and
- (p) nitro;

5

R⁴ is selected from:

- (a) hydrogen,
- (b) C₁₋₃alkyl, unsubstituted or substituted with 1-3 fluoro,
- 10 (c) -O-C₁₋₃alkyl, unsubstituted or substituted with 1-3 fluoro,
- (d) hydroxy,
- (e) chloro,
- (f) fluoro,
- (g) bromo, and
- 15 (h) phenyl;

R⁵ is selected from:

- (a) C₁₋₆alkyl, unsubstituted or substituted with 1-6 fluoro, hydroxyl, or both,
- 20 (b) -O-C₁₋₆alkyl, unsubstituted or substituted with 1-6 fluoro,
- (c) -CO-C₁₋₆alkyl, unsubstituted or substituted with 1-6 fluoro,
- (d) -S-C₁₋₆alkyl, unsubstituted or substituted with 1-6 fluoro,
- (e) -pyridyl, unsubstituted or substituted with one or more substituents
selected from: halo, trifluoromethyl, C₁₋₄alkyl, and COR¹¹,
- 25 (f) fluoro,
- (g) chloro,
- (h) bromo,
- (i) -C₄₋₆cycloalkyl, unsubstituted or substituted with 1-6 fluoro,
- (j) -O-C₄₋₆cycloalkyl, unsubstituted or substituted with 1-6 fluoro,
- 30 (k) phenyl, unsubstituted or substituted with one or more substituents selected from:
halo, trifluoromethyl, C₁₋₄alkyl, and COR¹¹,
- (l) -O-phenyl, unsubstituted or substituted with one or more substituents
selected from: halo, trifluoromethyl, C₁₋₄alkyl, and COR¹¹,
- (m) -heterocycle,
- 35 (n) -CN, and
- (o) -COR¹¹;

R⁶ is selected from:

- 40 (a) hydrogen,
- (b) C₁₋₃alkyl, unsubstituted or substituted with 1-3 fluoro,
- (c) -O-C₁₋₃alkyl, unsubstituted or substituted with 1-3 fluoro,

- 5 (d) hydroxy,
 (e) chloro,
 (f) fluoro,
 (g) bromo, and
 (h) phenyl;

R^7 is selected from:

- 10 (a) hydrogen,
 (b) (C₀₋₆alkyl)-phenyl,
 (c) (C₀₋₆alkyl)-heterocycle,
 (d) (C₀₋₆alkyl)-C₃₋₇cycloalkyl,
 (e) (C₀₋₆alkyl)-COR¹¹,
 (f) (C₀₋₆alkyl)-(alkene)-COR¹¹,
 15 (g) (C₀₋₆alkyl)-SO₃H,
 (h) (C₀₋₆alkyl)-W-C₀₋₄alkyl, where W is selected from: a single bond, - O-, -S-,
 -SO-, -SO₂-, -CO-, -CO₂-, -CONR¹²- and -NR¹²-,
 (i) (C₀₋₆alkyl)-CON R¹²-phenyl,
 (j) (C₀₋₆alkyl)-CON R¹⁵-V-CO R¹¹, where V is selected from C₁₋₆alkyl or
 20 phenyl, and
 (k) nothing, when X is O, S, or SO₂,

where:

- 25 R¹⁵ is hydrogen or C₁₋₄alkyl, or where R¹⁵ is joined via a 1-5 carbon tether to one of the carbons of V to form a ring,

C₀₋₆alkyl is unsubstituted or substituted with 1-5 substituents, where the substituents are independently selected from:

- 30 (a) halo,
 (b) hydroxy,
 (c) -C₀₋₆alkyl
 (d) -O-C₁₋₃alkyl,
 35 (e) trifluoromethyl, and
 (f) -C₀₋₂alkyl-phenyl,

phenyl, heterocycle, cycloalkyl, and C₀₋₄alkyl is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

- 40 (a) halo,
 (b) trifluoromethyl,
 (c) hydroxy,

- (d) C₁₋₃alkyl,
- (e) -O-C₁₋₃ alkyl,
- (f) -C₀₋₃-COR¹¹,
- (g) -CN,
- (h) -NR¹²R¹²,
- (i) -CONR¹²R¹², and
- (j) -C₀₋₃-heterocycle,

where the phenyl and heterocycle may be fused to another heterocycle, which itself may be unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -CO R¹¹, and -C₁₋₃alkyl, and where

alkene is unsubstituted or substituted with 1-3 substituents which are independently selected from:

- (a) halo,
- (b) trifluoromethyl,
- (c) C₁₋₃alkyl,
- (d) phenyl, and
- (e) heterocycle;

R⁸ is selected from:

- (a) hydrogen,
- (b) nothing when X is either O, S, SO₂ or N or when a double bond joins the carbons to which R⁷ and R¹⁰ are attached,
- (c) hydroxy,
- (d) C₁₋₆alkyl,
- (e) C₁₋₆alkyl-hydroxy,
- (f) -O-C₁₋₃alkyl,
- (g) -COR¹¹,
- (h) -CONR¹²R¹², and
- (i) -CN;

or where R⁷ and R⁸ may be joined together to form a ring which is selected from:

- (a) 1H-indene,
- (b) 2,3-dihydro-1H-indene,
- (c) 2,3-dihydro-benzofuran,
- (d) 1,3-dihydro-isobenzofuran,
- (e) 2,3-dihydro-benzothiofuran,
- (f) 1,3-dihydro-isobenzothiofuran,
- (g) 6H-cyclopenta[d]isoxazol-3-ol

- (h) cyclopentane, and
- (i) cyclohexane,

where the ring formed may be unsubstituted or substituted with 1-5 substituents independently selected from:

- (a) halo,
- (b) trifluoromethyl,
- (c) hydroxy,
- (d) C₁₋₃alkyl,
- (e) -O-C₁₋₃alkyl,
- (f) -C₀₋₃-COR¹¹,
- (g) -CN,
- (h) -NR¹²R¹²,
- (i) -CONR¹²R¹², and
- (j) -C₀₋₃-heterocycle;

or where R⁷ and R⁹ or R⁸ and R¹⁰ may be joined together to form a ring which is phenyl or heterocycle, wherein the ring is unsubstituted or substituted with 1-7 substituents independently selected from:

- (a) halo,
- (b) trifluoromethyl,
- (c) hydroxy,
- (d) C₁₋₃alkyl,
- (e) -O-C₁₋₃alkyl,
- (f) -COR¹¹,
- (g) -CN,
- (h) -NR¹²R¹², and
- (i) -CONR¹²R¹²;

R⁹ and R¹⁰ are independently selected from:

- (a) hydrogen,
- (b) hydroxy,
- (c) C₁₋₆alkyl,
- (d) C₁₋₆alkyl-COR¹¹,
- (e) C₁₋₆alkyl-hydroxy,
- (f) -O-C₁₋₃alkyl,
- (g) =O, when R⁹ or R¹⁰ is connected to the ring via a double bond
- (h) halo;

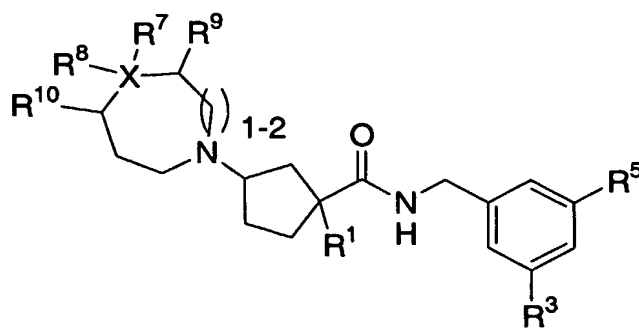
R¹⁶ selected from:

- (a) hydrogen,
 (b) phenyl,
 5 (c) C₁₋₆alkyl which may be substituted or unsubstituted with 1-6 of the following substituents: -COR¹¹, hydroxy, fluoro, chloro, -O-C₁₋₃ alkyl;

the dashed line represents a single or a double bond;

10 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. A compound of Claim 1 of formula Ia:

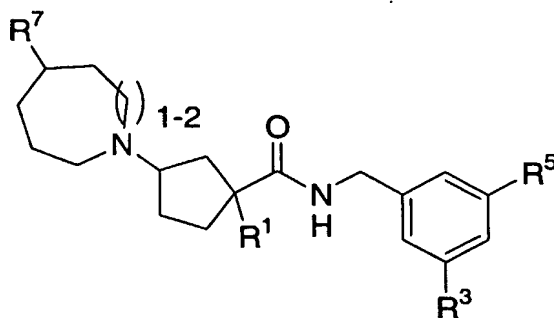


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Ia

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. A compound of Claim 1 of formula Ib:

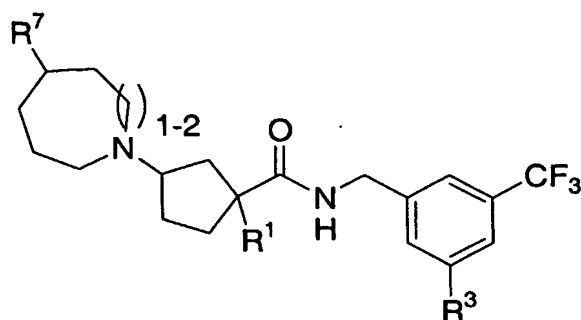


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Ib

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

4. A compound of Claim 1 of formula Ic:



Ic

- 5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5. The compound of claim 1, wherein X is N, O, or C.

6. The compound of claim 1, wherein R¹ is selected from -C₁₋₆alkyl, -C₀₋₆alkyl-O-C₁₋₆alkyl, heterocycle, and -(C₀₋₆alkyl)-(C₃₋₇cycloalkyl)-(C₀₋₆alkyl),

where the alkyl, heterocycle, and the cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- (c) -O-C₁₋₃alkyl,
- (d) trifluoromethyl,
- (f) C₁₋₃alkyl,
- (g) -O-C₁₋₃alkyl,
- (h) -COR¹¹,
- (i) -CN,
- (j) -NR¹²R¹²,
- (k) -CONR¹²R¹², and
- (j) -NCOR¹³.

7. The compound of claim 1, wherein R¹ is:

-C₁₋₆alkyl, unsubstituted or substituted with 1-6 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- (c) -O-C₁₋₃alkyl,
- (d) trifluoromethyl, and

(e) $-\text{COR}^{11}$;

$-\text{C}_0\text{-6alkyl-O-C}_1\text{-6alkyl-}$, which is unsubstituted or substituted with 1-6 substituents independently selected from:

- (a) halo,
 (b) trifluoromethyl, and
 (c) $-\text{COR}^{11}$;

$-(\text{C}_3\text{-5cycloalkyl})-(\text{C}_0\text{-6alkyl})$, which is unsubstituted or substituted with 1-7 substituents independently selected from:

- (a) halo,
 (b) hydroxy,
 (c) $-\text{O-C}_1\text{-3alkyl}$,
 (d) trifluoromethyl, and
 (e) $-\text{COR}^{11}$; and

heterocycle, unsubstituted or substituted with $-\text{NCOR}^{13}$ or $-\text{NR}^{12}\text{R}^{12}$.

8. The compound of claim 1, wherein R^1 is selected from:

- (a) $\text{C}_1\text{-6alkyl}$,
 (b) $\text{C}_1\text{-6alkyl}$ substituted with hydroxy,
 (c) $\text{C}_1\text{-6alkyl}$ substituted with 1-6 fluoro, and
 (d) thiazole, unsubstituted or substituted with $-\text{NHCOR}^{13}$.

9. The compound of claim 1, wherein R^1 is selected from:

- (a) $-\text{CH}(\text{CH}_3)_2$,
 (b) $-\text{C}(\text{OH})(\text{CH}_3)_2$,
 (c) $-\text{CH}(\text{OH})\text{CH}_3$,
 (d) $-\text{CH}_2\text{CF}_3$, and
 (e) -thiazole, bonded to the core at the 4 position of the thiazole ring, unsubstituted or substituted with $-\text{NHCOCH}_3$ at the 2 position of the thiazole ring.

10. The compound of claim 1, wherein R^2 is hydrogen.

11. The compound of claim 1, wherein R^3 is selected from:

- (a) hydrogen,
 (b) halo,
 (c) hydroxy,
 (d) $\text{C}_1\text{-3alkyl}$, where the alkyl is unsubstituted or substituted with 1-6 substituents independently selected from: fluoro, and hydroxy,

- (e) -COR¹¹,
- (f) -CONR¹²R¹²,
- (g) -heterocycle,
- (h) -NR¹²-SO₂-NR¹²R¹²,
- (i) -NR¹²-SO₂-R¹⁴,
- (j) -SO₂-NR¹²R¹²,
- (k) -nitro, and
- (l) -NR¹²R¹².

12. The compound of claim 1, wherein R³ is selected from:

- (a) hydrogen,
- (b) fluoro, and
- (c) trifluoromethyl.

13. The compound of claim 1, R³ is selected from fluoro and trifluoromethyl.

14. The compound of claim 1, wherein R⁴ is hydrogen.

15. The compound of claim 1, wherein R⁵ is selected from:

- (a) C₁₋₆alkyl substituted with 1-6 fluoro,
- (b) -O-C₁₋₆alkyl substituted with 1-6 fluoro,
- (c) chloro,
- (d) bromo, and
- (e) phenyl.

16. The compound of claim 1, wherein R⁵ is selected from:

- (a) trifluoromethyl,
- (b) trifluoromethoxy,
- (c) chloro,
- (d) bromo, and
- (e) phenyl.

17. The compound of claim 1, wherein R⁵ is trifluoromethyl.

18. The compound of claim 1, wherein R⁶ is hydrogen.

19. The compound of claim 1, wherein R⁷ is selected from phenyl, heterocycle, C₃₋₇cycloalkyl, C₁₋₆alkyl, -COR¹¹, and -CONH-V-COR¹¹,

where V is selected from C₁₋₆alkyl or phenyl, and

where the phenyl, heterocycle, C₃₋₇cycloalkyl, and C₁₋₆alkyl is unsubstituted or substituted with 1-5 substituents independently selected from:

- 5 (a) halo,
- (b) trifluoromethyl,
- (c) hydroxy,
- (d) C₁₋₃alkyl,
- (e) -O-C₁₋₃alkyl,
- 10 (f) -COR¹¹,
- (g) -CN,
- (h) -heterocycle, and
- (i) -CONR¹²R¹².

- 15 20. The compound of claim 1, wherein R⁷ is selected from phenyl, heterocycle, C₁₋₄alkyl, -COR¹¹, and -CONH-V-COR¹¹,

where V is selected from C₁₋₆alkyl or phenyl, and

- 20 where the phenyl, heterocycle, and C₁₋₄alkyl is unsubstituted or substituted with 1-3 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- 25 (c) C₁₋₃alkyl,
- (d) -O-C₁₋₃alkyl,
- (e) -COR¹¹, and
- (f) -heterocycle.

- 30 21. The compound of claim 1, wherein R⁷ is selected from:

- (a) hydrogen,
- (b) -COR¹¹,
- (c) -CONHCH₃,
- 35 (d) phenyl,
- (e) heterocycle,

22. The compound of claim 1, wherein when X is C, R⁸ is selected from:

- 40 (a) hydrogen,
- (b) hydroxy,
- (c) -CN, and
- (d) -F.

- 45 23. The compound of claim 1, wherein R⁸ is hydrogen.

24. The compound of claim 1, wherein R^7 and R^8 may be joined together to form a ring which is selected from 1H-indene and 2,3-dihydro-1H-indene,

5 where the ring formed may be unsubstituted or substituted with 1-3 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- 10 (c) C_{1-3} alkyl,
- (d) $-O-C_{1-3}$ alkyl,
- (e) $-COR^{11}$, and
- (f) -heterocycle.

15 25. The compound of claim 1, wherein R^9 and R^{10} are independently selected from:

- (a) hydrogen,
- (b) hydroxy,
- 20 (c) $-CH_3$,
- (d) $-O-CH_3$, and
- (e) $=O$, where R^9 and/or R^{10} are joined to the ring via a double bond.

25 26. The compound of claim 1, wherein R^9 and R^{10} are hydrogen.

27. The compound of claim 1, wherein R^{16} is hydrogen.

28. A pharmaceutical composition which comprises an inert carrier and a
30 compound of Claim 1.

29. A method for modulation of chemokine receptor activity in a mammal
which comprises the administration of an effective amount of a compound of Claim 1.

30 30. A method for treating, ameliorating, controlling or reducing the risk of an
35 inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

31. A method for treating, ameliorating, controlling or reducing the risk of
40 rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.